

ARIC Manuscript Proposal # 735

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Priority: 1
Priority: 1

1.a. Full Title: Retinal microvascular abnormalities and coronary heart disease: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Retinal abnormalities and CHD

2. Writing Group (list individual with lead responsibility first):

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3. Timeline:

This analysis is part of overall objective to investigate the association between cardiovascular diseases and retinal microvascular abnormalities based on photographic grading during the ARIC third examination. Specifically, this proposal will be similar to ARIC #553 (Retinal microvascular changes and Incident strokes), with a new dataset created for incident CHD events. We estimate about 277 incident CHD cases between ARIC visit 3 to December 1997, among about 9,500 participants with gradable retinal photographs. The proposal will be different from ARIC #540 (Diabetic retinopathy and CHD), which will evaluate the cross-sectional association between CHD and CHD risk factors (among other variables such as glycemic control) and diabetic retinopathy (as the primary endpoint).

After approval, the initial analyses and writing will take place between August 2000 and Dec 2000 (based on incident CHD cases identified up to Dec 1997), with final analysis between Jan 2001 and June 2001 (with further inclusion of incident CHD cases up to Dec 1998, if necessary), and final writing and submission of manuscript between July 2001 and September 2001.

4. Rationale:

CHD is the leading cause of mortality and morbidity in the United States. Although coronary atherosclerosis is the major cause of CHD, there are data that suggest coronary microvascular pathology (such as coronary arteriolosclerosis) may contribute significantly to both CHD risk and mortality. Epidemiological studies indicate that coronary microvascular disease appears to be associated with increased 1) risk of CHD in the absence of overt epicardial coronary artery blockage, 2) risk of congestive heart failure after myocardial infarction, and 3) mortality in persons with a history of prior CHD. Studies have also shown that in persons with

hypertension and diabetes, the presence of microvascular disease (manifested elsewhere in the body) is associated with increased risk of silent MI and increased CHD mortality.

As microvascular abnormalities in the retina (e.g. arterio-venous nicking, arteriolar narrowing and retinopathy) reflect systemic microvascular damage from hypertension, and are accessible to direct non-invasive evaluation, they have been suggested as potential markers of CHD risk.

However, limited data on the association between retinal microvascular abnormalities and CHD exist, with some studies reporting inconsistent associations, and others not finding any. In a large cross-sectional study based on data from the National Health Examination Survey, retinal microvascular abnormalities detected on ophthalmoscopy were associated with a four- to six-fold increase in prevalent CHD in participants aged 35 to 54 years, after controlling for hypertension, diabetes and serum cholesterol levels. The strength of association was weaker for men than women, and for older compared to younger persons. However, the data were cross-sectional, and the detection and definition of the retinal lesions were ambiguous, based on clinical ophthalmoscopy, a technique that has been shown to be subjective and unreliable. Other studies that described associations suffered from similar limitations.

In ARIC, retinal microvascular abnormalities were quantified based on standardized photographic grading techniques and on computer-assisted measurements of retinal arteriole calibers. We found that retinal microvascular abnormalities were related strongly and monotonically not only with current blood pressure levels, but with past blood pressure levels independent of current blood pressure. In addition, these abnormalities were shown to be associated with prevalent subclinical stroke detected on MRI among persons with hypertension (OR ranging from 2 to 3), and with incident clinical strokes (RR ranging from 1.5 to 3), independent of mean blood pressure levels over the three ARIC examinations and other stroke risk factors.

The purpose of this present proposal is to evaluate the relation between retinal microvascular abnormalities and incident CHD in the ARIC population.

5. Main Hypothesis/Study Questions:

- (1) After controlling for age, sex, race, dyslipidemia, blood pressure, smoking, diabetes, obesity, activity, family history of CVD, and additional CVD risk factors, retinal microvascular abnormalities are associated independently with increased risk of CHD.
- (2) The association of these abnormalities with CHD is different for fatal versus non-fatal CHD, for silent versus clinical MI, and for MI with versus without congestive heart failure.
- (3) The association of these abnormalities with CHD is stronger in younger versus older persons, women versus men, person with versus without hypertension, and persons with versus without diabetes

6. Data (variables, time window, source, inclusions/exclusions):

- (1) Retinal variables: Focal retinal microvascular changes include arteriovenous nicking, focal arteriolar narrowing, any retinopathy, retinal hemorrhage and type of hemorrhage (flame-shaped and blot hemorrhage), microaneurysm, soft exudates and hard exudates. Generalized arteriolar narrowing quantified as branch retinal arteriole-to-venular ratio (AVR), central retinal arteriolar equivalent, central retinal venular equivalent.
- (2) Incident CHD variables: Censoring variables (all CHD, acute MI, silent MI, other non-MI CHD, fatal CHD, nonfatal CHD). Time to event for each censoring variable (defined as time from visit 3 to either CHD event or censoring)
- (3) Demographic variables: age at visit 3, sex, race, center

- (4) Other CVD risk factors/potential confounders: Hypertension status, diabetes status, mean arterial BP, systolic and diastolic BP, serum lipids (total, HDL and LDL cholesterol, TG, lp(a), apo A1 and B, fasting glucose levels, hemostatic function indicators (von Willebrand factor, factor VIIIC, fibrinogen, WBC, cigarette smoking indicators (ever/never, current/former/never, pack-years), alcohol indicators, hypertensive medications, diabetic medications, body mass index, waist to hip ratio, sports/leisure/work index, family history of CVD and Aspirin use (variables from ARIC visit 1-3, except for lp(a), apo A1 and B, von Willebrand factor, factor VIIIC, and cigarette pack-years, available from ARIC visit 1 only)
- (5) Exclusion criteria: From participants at ARIC third exam, exclude persons who did not participate in the second exam, whose race is neither black nor white, if missing data on BP, hypertension status, hypertensive medications, smoking history, and plasma cholesterol at any of the three examinations. Also exclude persons with no retinal photographs or upgradeable photographs and those with retinal venous or artery occlusions. Finally exclude persons with either prevalent CHD at baseline, or incident CHD between baseline and visit 3.

7.a. Will the data be used for non-CVD analysis in this manuscript? ☐ Yes ☒ No

b. If Yes, is the author aware that the file ICTDER01 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ☐ Yes ☐ No

(This file ICTDER01 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ☐ Yes ☒ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ☐ Yes ☐ No